Perinatal Dopamine-Related Drugs Demasculinize Rats

Abstract. Administration of haloperidol, a common neuroleptic, to pregnant or lactating rats impaired the masculine sex behavior of their male offspring. Prenatal haloperidol did not affect testosterone concentrations in fetuses. Maternal administration of apomorphine, a dopamine agonist, and of a-methyl-p-tyrosine, an inhibitor of dopamine synthesis, also demasculinized male offspring. In both experiments other behaviors and developmental milestones were unaffected. Perinatal haloperidol, apomorphine, and a-methyl-p-tyrosine did not lower testosterone in adulthood. These drugs may act directly on neurons that control masculine behavior without lowering testosterone prenatally or in adulthood.

Perinatal administration of certain drugs or hormones produces lasting impairment of reproductive function and sexual behavior in male rodents (1-4). Several of these agents appear to exert their demasculinizing effects by reducing the concentration of testosterone perinatally or in adulthood (2, 3, 5, 6). While high concentrations of testosterone during the week before and the week after birth appear to be critical for sexual differentiation (7), the mechanisms by which testosterone exerts its masculinizing effects have not been identified.

One possible mechanism of testosterone action involves a direct effect on developing neurons through alterations in growth, synaptogenesis, receptors, or enzyme activity. Monoaminergic neurons have been shown to regulate the expression of sex behavior in adulthood, with dopamine (DA) facilitating (8, 9) and serotonin inhibiting masculine behavior (9, 10). Alterations in monoaminergic activity may also play a role in the developmental demasculinizing effects noted above. Because DA is the only monoamine shown to facilitate masculine behavior in adulthood, we investigated the effects of several perinatally administered drugs that affect DA transmission.

Haloperidol (HAL) blocks DA receptors preferentially though not exclusively and crosses placental and lactational barriers (11). Rosengarten and Friedhoff (12) reported that administration of HAL to pregnant rats depressed binding of [3H]spiroperidol in the brains of their offspring as late as 60 days of age. Behavioral responsiveness of the offspring to apomorphine (APO), a DA agonist, was also depressed by perinatally administered HAL. On the other hand, neonatal treatment with HAL (through lactation) had the opposite effect, increasing [3H]spiroperidol binding and behavioral responsiveness to APO. This is similar to the supersensitivity to DA seen in adult animals after long-term treatment with neuroleptics. Because DA facilitates adult masculine sex behavior, we hypothesized that prenatally administered HAL would impair masculine behavior in adulthood, that neonatal treatment with HAL would facilitate it, and that combined pre- and neonatal treatments would tend to cancel these effects.

Ten Long-Evans female rats were mated and divided into two groups that were injected intraperitoneally with HAL (2.5 mg/kg) or saline from day 7 of gestation until day 21 postpartum, except on the day of birth. Treatment parameters were the same as those shown by Rosengarten and Friedhoff (12) to
affect receptor binding and behavioral stereotypy. Half the pups of each litter were cross-fostered on the day of birth to a mother receiving the opposite treatment. Thus four treatment groups were formed: one receiving HAL both pre- and postnatally (HH; 8 males and 7 females), one receiving HAL prenatally only (HS; 7 males and 6 females), one receiving HAL postnatally only (SH; 9 males and 12 females), and one receiving saline only (SS; 10 males and 11 females).

We tested male offspring for masculine sexual behavior with a receptive female at 65, 72, and 79 days of age (13). In test 1 (day 65), males in all three drug groups (HH, HS, and SH) had significantly fewer ejaculations than the control animals (Fig. 1a). However, in test 2 (day 79), only prenatally treated animals (groups HH and HS) exhibited a significant deficit. There was no statistically significant difference among groups in the percentage of animals achieving at least one intromission. Thus the "arousal mechanism" leading to the onset of copulation (14) was not impaired. However, the perinatal drug treatments significantly reduced the probability of ejaculation among males that intromitted (50, 53, 71, and 87 percent in groups HH, HS, SH, and SS, respectively) \( \chi^2(3) = 14.01, P < 0.01 \) (15). This suggests a deficit in the "copulatory mechanism," which is thought to summate the effects of repeated intromissions until an ejaculation is triggered (14). Among animals that had achieved at least one ejaculation there were no significant treatment-related differences in any copulatory measure. Thus perinatal HAL reduced the number of males able to achieve ejaculation once they began intromitting.

There were no statistically significant differences in feminine sexual behavior among groups of female offspring (16). Also unaffected were open field ambulation (in both sexes) at 20, 40, and 80 days of age; age at eye opening or testicular descent; and HAL-induced catalepsy at 90 days of age (17). The only statistically significant difference in body weight was observed on postnatal day 8, when HH and HS females were lighter than SS and SH females \( F(3, 27) = 4.31, P < 0.05 \). Thus, the drug treatment did not debilitate the pups or delay their maturation. Furthermore, since HH and HS males exhibited similar deficits, drug-induced alteration of maternal behavior was not a major factor producing the deficits.

To determine whether a depression of fetal testosterone might have mediated the demasculinization, we treated additional groups of five females each with HAL (2.5 mg/kg) or saline on days 7 to 18 of gestation. Concentrations of testosterone (18) on day 18 [the day of peak testosterone (7)] were not significantly different between groups.

Since blocking DA receptors pre- or neonatally impaired male sex behavior in adulthood, we designed a second experiment to test the effects of facilitating DA transmission perinatally with APO. Furthermore, since HAL, in addition to blocking DA receptors, also increases DA synthesis, we wished to inhibit DA synthesis in another group of animals. Therefore, we administered \( \alpha \)-methyl-p-tyrosine methyl ester (\( \alpha \)-MT; 60 mg/kg to inhibit DA synthesis) to one group of mother rats, APO (1 mg/kg to facilitate DA transmission) to another, both \( \alpha \)-MT and APO to a third, and the saline vehicle to a fourth. Drugs were administered from day 13 of gestation to postnatal day 21, except on the day of birth; each litter received the same treatment pre- and postnatally. There were ten male offspring in the \( \alpha \)-MT group, ten in the APO group, nine in the group that received both \( \alpha \)-MT and APO, and nine in the control group.

To assess the relative importance of maturational age and sexual experience in any improvement in sexual behavior that might occur across the three tests, we tested half the males of each litter at 60, 75, and 90 days of age and half on days 90, 105, and 120. There were no statistically significant differences between the 60-day series and the 90-day series for any group; therefore, all animals in each treatment group were combined for further statistical analyses. As seen in Fig. 1b, control males achieved more ejaculations on tests 2 and 3 than did males in the three drug groups. Among males that ejaculated in test 3, control males ejaculated sooner than males in any of the drug groups; the drug groups did not differ significantly among themselves (Fig. 1c). As in the first experiment, the decreased number of ejaculations was related to a decreased probability of ejaculation in animals that intromitted (67, 55, 67, and 93 percent in the \( \alpha \)-MT, APO, \( \alpha \)-MT + APO, and saline groups, respectively) \( \chi^2(3) = 10.94, P < 0.02 \) rather than to a reduced probability of intromitting at all (19)

After being tested for sexual behavior, the animals were tested for APO-induced stereotypy and HAL-induced catalepsy (20). Scores on these measures did not differ significantly among groups and were not correlated with number of ejaculations. Furthermore, differences in sexual behavior could not be attributed to general malnutrition or to delayed development of the drug-treated ani-
The modes of action of perinatally administered drugs are multifaceted and are not well understood. Several drugs reported to demasculinize rodents have been found to reduce testosterone peri-

naturally or during adulthood. However, the lack of such suppression by HAL on fetal testosterone or by any of our perinatally administered drugs on adult testo-

sterone appears to rule out simple changes in androgen levels as a factor in our results.

One possible mechanism may be altered neuronal growth or function. It has been suggested that the presence of monoamines one week before they are needed for synaptic transmission implies their use as trophic substances (21). Inter-

ference with monoamine activity peri-

naturally has been reported to impair sev-

eral measures of neuronal maturat-

ion (22). We suggest that the demasculin-

izing effects of perinatally administered drugs may be exerted directly on the neurons that regulate sexual behavior in adulthood and that these effects do not require a reduction of testosterone peri-

naturally or in adulthood. Furthermore, since the alterations in receptor binding induced by prenatal HAL decreased steadily from 28 to 60 days of age (12), sexual impairment as late as 120 days of age may be related to permanently changed patterns of neural growth, syn-

aptogenesis, or some factor other than receptor binding.

Drug effects on the monoamines are widely prescribed for psychological dis-

orders, hypotension, and emesis. Re-

stricted drug intake is frequently advised during the first trimester of pregnancy, when major fetal organs are forming. However, neuronal growth and synap-

togenesis occur later and continue after birth. Evidence of enduring behavioral deficits resulting from perinatal drug treatment in rats suggests caution in treating women with such drugs during pregnancy or lactation.

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mones).


13. Males were tested in their home cages with a recorded female for 30 minutes after the first intormission. Latency to each mount, intromis-

sion, and ejaculation was recorded. Interruption by each mount, ejaculation, and latency to first postejaculatory intromission were calculated. 13. F. A. Beach, in Nebraska Symposium on Moti-

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14. HH animals intromitted in 18 tests and ejaculated in 9 of them. HS animals intromitted in 17 tests and ejaculated in 9. SH animals intromitted in 15 of 21 tests with intromissions. SS animals ejaculated in 26 of 30 tests with intromissions.

15. Overactive males were injected with 4 μg of estradiol benzoate 48 and 24 hours before a test and with 500 μg of progesterone 4 hours before the test. Liddos normal rats on a 4-

point scale were averaged over ten attempted mounts by the male on each of three weekly tests.

16. In the open field ambulation was measured by the number of lines crossed in 10 minutes in a 1-m2 box divided by the number of lines in the 15-cm-high cage. The forepaws were placed on the 15-cm-high edge of the cage. The total number of seconds that the rat maintained this position over four tests was calculated.

17. Assays were performed with the technique of Dalterio and Bartke (5).

18. Animals given o-MT intromitted in 39 tests and ejaculated in 26 of those. Animals given APO intromitted in 49 tests and ejaculated in 47. Animals given α-MT plus APO intromitted in 46 tests and ejaculated in 31. Control rats ejaculated in 39 of 42 trials with an intromission rate of 1.5 intromissions per ejaculation and were placed on a line 13 cm behind and parallel to a plastic cage. The male was tested in the 15-cm-high box and the total number of seconds that the rat maintained this position over four tests was measured.

19. Supported in part by NIH grants HD 16329 to S. D. and by biomedi-

cal research support grant 2S07RR0706618 to S. D. and by NIH grants HD 16329 to S. D. and by biomedi-

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12. Supported in part by NIH grants MH 3593901 to E. M. H. and HD 16329 to S. D. and by biomed-

ical research support grant 250758/700616 to E. M. H. We thank McNeil Pharmaceutical Co. for the gift of Halodol and A. P. Shah, L. A. Pehek, J. A. Craja, C. J. Smith, and R. T. Hull for helpful comments on the manuscript.


14. Supported in part by NIH grants MH 3593901 to E. M. H. and HD 16329 to S. D. and by biomed-

ical research support grant 250758/700616 to E. M. H. We thank McNeil Pharmaceutical Co. for the gift of Halodol and A. P. Shah, L. A. Pehek, J. A. Craja, C. J. Smith, and R. T. Hull for helpful comments on the manuscript.

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11 October 1983; accepted 9 April 1984